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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/571,991

03/15/2006

Laurent Francois Andre Hennequin

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08/26/2010

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EXAMINER

WILLIS, DOUGLAS M

ART UNIT

PAPER NUMBER

1624

MAIL DATE

DELIVERY MODE

08/26/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/571,991	Applicant(s) HENNEQUIN ET AL.	
	Examiner DOUGLAS M. WILLIS	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 March 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 38-43 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 38-43 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>03-30-10</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

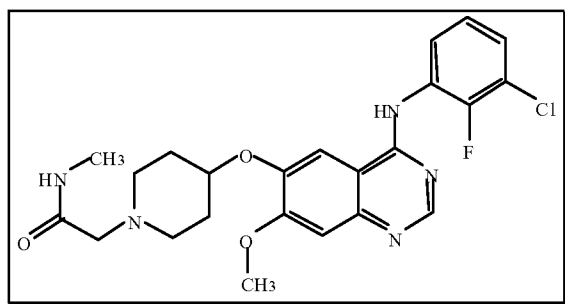
Status of the Claims / Priority

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the *Final Rejection*, mailed on November 27, 2009, has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission, filed on March 30, 2010, has been entered.

Claims 38-43 are pending in the current application. According to the *Amendments to the Claims*, filed April 6, 2009, claims 39, 40, 42 and 43 were amended and claims 1-37 and 44-71 were cancelled. This application is a 35 U.S.C. § 371 National Stage Filing of International Application No. PCT/GB2004/03937, filed September 15, 2004, which claims priority under 35 U.S.C. § 119(a-d) to: a) EP 03292309.6.7, filed September 19, 2003; and b) EP 04291248.5, filed May 14, 2004.

Status of Restrictions / Election of Species

Applicant's affirmation of the following election, without traverse, in the reply filed on



December 11, 2008, is acknowledged: a) Group I, claims 38-43; and b) substituted quinazolinamine - p. 58, example 1, shown to the left, and hereafter referred to as 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline.

The requirement was made FINAL in the *Final Rejection*, mailed on January 6, 2009.

The sections of U.S.C. Title 35 that formed the basis of prior rejections formulated, as well as any references supporting said rejections, that are not included with this Office action, may be found in either the *Non-Final Rejection*, mailed on August 19, 2008, the *Final Rejection*, mailed on January 6, 2009, the *Non-Final Rejection*, mailed on May 26, 2009, or the *Final Rejection*, mailed on November 27, 2009. Furthermore, any rejections and/or objections of record not explicitly addressed herein below, are hereby withdrawn, in light of applicant's arguments, filed March 30, 2010, and/or the *Amendments to the Claims*, filed April 6, 2009.

Thus, a fifth Office action and prosecution on the merits of claims 38-43 is contained within.

Status of Claim Rejections - 35 U.S.C. § 103

Applicant's arguments, on pages 2-8 of the *Remarks*, filed March 30, 2010, with respect to claims 38-43, have been fully considered, but are not persuasive. Consequently, the rejection of claims 38-43, made in the *Final Rejection*, mailed on November 27, 2009, is hereby maintained for the reasons of record.

Applicant primarily argues that the Office has failed to make a reasoned identification of a lead compound. Moreover, applicant further argues that the Office has failed to identify a reason to make the requisite modification to example 38.

In response to applicant's arguments that (1) the Office has failed to make a reasoned identification of a lead compound, and that (2) the Office has failed to identify a reason to make the requisite modification to example 38, the examiner respectfully disagrees, since, MPEP § 2144-I states that *the rationale to modify or combine the prior art does not have to be expressly*

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stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. {See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)}.

Similarly, in response to applicant's arguments that (1) the Office has failed to make a reasoned identification of a lead compound, and that (2) the Office has failed to identify a reason to make the requisite modification to example 38, the examiner further respectfully disagrees, since, the Takeda decision differs considerably in its facts from the facts presented herein. The prior art compound relied on by the examiner in that case was documented in more than one reference and by expert witnesses as having serious side-effects that would be deleterious for its intended purpose. It is the examiner's position that applicant is confusing *negative* properties which existed for *compound b* in Takeda with *different* properties which applicants urge exist for their compounds versus the prior art compounds of reference. Possessing *different* properties is not enough to defeat obviousness where compounds are very similar in structure and otherwise there is a suggestion to modify in the prior art as is the case presented herein. The former situation based on the totality of facts present rendered a decision which in that case led to disqualification of the prior art compound based on *reasonable expectation of success* in

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performing the intended use.

Moreover, in response to applicant's arguments that (1) the Office has failed to make a reasoned identification of a lead compound, and that (2) the Office has failed to identify a reason to make the requisite modification to example 38, the examiner further respectfully disagrees, since, in *Eisai*, the focus of the prior art rejection in that case was on a compound known in the prior art to have a desirable property (i.e. *lipophilicity*) based on the presence of a trifluoroethoxy group, which was the identical site necessary to be modified to arrive at patentee's compound. Thus, a *teach away* aspect was present which was not cured by any of the secondary references applied. In fact, in the *Eisai* case, the court made a statement (at p.1456) that the *district court did not rigidly limit Teva's obviousness arguments by forcing Teva to select a **single** (bold emphasis added) lead compound.*

It is the examiner's position that the prior art of record lacks a *teach away* aspect. Applicant should further direct their attention to MPEP § 2141.02-VI which not only relates to references that may *teach away*, but also states that alternative embodiments should **not** be confused with *teaching away*, citing *In re Fulton* at 73 USPQ2d 1141: *The prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed in the '198 application. Indeed, in the case cited by appellants, In re Gurley, we held that the invention claimed in the patent application was unpatentable based primarily on a prior art reference that disclosed two alternatives, one of which was the claimed alternative. Accordingly, mere disclosure of alternative designs does not teach away.*

Applicant should note that a *prima facie* case of obviousness based on structural

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similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. {See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967); and *In re Peterson*, 65 USPQ2d 1379 (Fed. Cir. 2003)}.

As a result of the *Amendments to the Claims*, filed April 6, 2009, and to clarify the record, the original rejection, made in the *Non-Final Rejection*, mailed on May 26, 2009, is amended below, in the section entitled *New Claim Rejections - 35 U.S.C. § 103*.

New Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

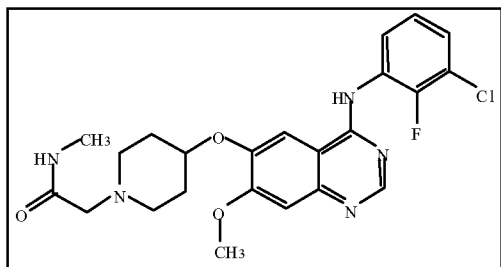
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 38-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Himmelsbach, et al. in US 6,924,285.

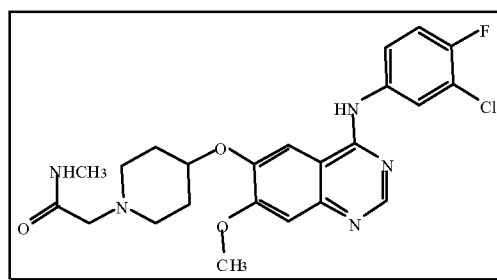
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The instant application recites 4-(3-chloro-**2-fluoro**anilino)-7-methoxy-6-{{1-(*N*-methyl-



carbamoylmethyl)piperidin-4-yl]oxy}quinazoline, shown to the left, and a pharmaceutically acceptable salt or pharmaceutical composition thereof, as an anti-tumor agent.

Himmelsbach, et al. (US 6,924,285), as cited on the IDS, teaches 4-(3-chloro-4-**fluoro**anilino)-7-methoxy-6-{{1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, shown to the right, and a physiologically acceptable salt or pharmaceutical composition thereof, as a therapeutic agent for treating tumoral diseases [columns 69 and 70, compound 38; physiologically acceptable salts - column 18, lines 41-48; and pharmaceutical compositions - column 1, lines 17-18]. Moreover, in the genus disclosure, Himmelsbach discloses that *p*-fluoro and *o*-fluoro are alternatively usable on the anilino ring at C-4 of the quinazoline core [*R*^b: column 1, lines 53-54; and *R*¹-*R*³: column 1, line 56 - column 2, line 3].



The only difference between the instantly recited 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(*N*-methyl-carbamoylmethyl)piperidin-4-yl]oxy}quinazoline and Himmelsbach's 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{1-(*N*-methylcarbamoylmethyl)piperidin-4-yl]oxy}-quinazoline is the instantly recited 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(*N*-methyl-carbamoylmethyl)piperidin-4-yl]oxy}quinazoline has an *o*-F on the anilino ring at C-4 of the quinazoline core, whereas Himmelsbach's 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{1-(*N*-methylcarbamoyl-methyl)piperidin-4-yl]oxy}quinazoline has a *p*-F on the anilino ring at C-4 of

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the quinazoline core.

In the chemical arts, it is widely accepted that *structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions or compounds, creates a prima facie case of obviousness.* {See *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, No. 06-1329, slip op. at 9 (Fed. Cir. June 28, 2007) (quoting *In re Dillon*, 919 F.2d 688, 692 [16 USPQ2d 1897] (Fed. Cir. 1990) (en banc)); and *In re Papesch*, 315 F.2d 381 [137 USPQ 43] (C.C.P.A. 1963)}.

Consequently, since: a) Himmelsbach teaches 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{1-(N-methylcarbamoylmethyl)piperidin-4-yl}oxy}quinazoline, where *p*-F is bonded to the anilino ring at C-4 of the quinazoline core; b) Himmelsbach teaches that 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{1-(N-methylcarbamoylmethyl)piperidin-4-yl}oxy}quinazoline and 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{1-(N-methylcarbamoylmethyl)piperidin-4-yl}oxy}quinazoline are alternatively usable; and c) the courts have recognized that *structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions or compounds, creates a prima facie case of obviousness*, one having ordinary skill in the art, at the time this invention was made, would have been motivated to utilize the teachings of Himmelsbach and replace the *p*-F of the anilino ring at C-4 of the quinazoline core in Himmelsbach's 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-{{1-(N-methylcarbamoylmethyl)piperidin-4-yl}oxy}quinazoline with an alternatively usable *o*-F, and formulate a pharmaceutically acceptable salt or pharmaceutical composition thereof, with a reasonable expectation of success and similar

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therapeutic activity, rendering claims 38-43 obvious.

Finally, although not explicitly discussed herein, applicant is advised to note that the Himmelsbach reference contains additional species that may obviate the instantly recited 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline. Consequently, any amendments to the claims and/or arguments formulated to overcome rejections rendered under 35 U.S.C. § 103(a) should address this reference as a whole and should not be limited to the species discussed or disclosed explicitly herein.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Allowable Subject Matter

No claims are allowed.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action

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after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DOUGLAS M. WILLIS, whose telephone number is 571-270-5757. The examiner can normally be reached on Monday thru Thursday from 8:00-6:00 EST. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/DOUGLAS M WILLIS/
Examiner, Art Unit 1624

**/James O. Wilson/
Supervisory Patent Examiner, AU 1624**